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The Origin of Mosaic Down Syndrome: Four Cases with Chromosome Markers

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SUMMARY

Four children, a girl and three boys, with diploid/trisomic mosaic Down syndrome were studied for the mechanism of origin of mosaics, using Q- and R-banding heteromorphisms as markers. Three mosaic subjects started as a trisomic zygote followed by the loss of a chromosome 21 at an early mitotic division. Of these, one resulted from a maternal first-meiotic error, another resulted from a paternal first-meiotic event, and the third originated from a first-meiotic error in either parent. The remaining subject could have resulted from either a diploid or a trisomic zygote. These findings, together with a higher proportion of trisomic cells in skin fibroblasts than in peripheral blood lymphocytes in the two patients studied, suggest that the extra chromosome 21 in mosaic Down syndrome patients usually has a meiotic origin. At least two, possibly three, of the diploid cell lines in these mosaics consisted of "uniparental" chromosomes 21, namely, both the homologous members were derived from a parent.

INTRODUCTION

It is generally accepted that approximately 1%–2% of all live-born Down syndrome individuals are mosaics. While a number of Down syndrome individuals have been studied for the origin of the extra chromosome 21, using chromosomal heteromorphisms as markers [1], there is no such study on mosaic Down syndrome individuals. Phenotypically normal mosaic parents of Down syndrome children have been studied for their origin in two families, but the results were inconclusive [2, 3].

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While it is frequently assumed that the extra chromosome 21 in mosaic Down syndrome individuals arises from mitotic nondisjunction in a chromosomally normal zygote, evidence from maternal ages [4] suggests that a large proportion of such cases arise from meiotic nondisjunction. Our report deals with the origin of four diploid/trisomic mosaic subjects with Down syndrome.

MATERIALS AND METHODS

The subjects studied included four children with diploid/trisomic mosaic Down syndrome, a girl and three boys, ages 5 days to 2 yrs 9 mos.

Air-dried chromosome preparations were made from the subjects and their parents. Chromosomal heteromorphisms were analyzed using a sequential Q- and R-banding method [5]. Analysis of the mode of inheritance of informative chromosomes was performed as described [6, 7].

Repeat lymphocyte cultures were analyzed from each subject, with irregular intervals over periods up to 15 months, to detect possible longitudinal changes of the proportion of diploid and trisomic cell lines. Both conventionally stained and G-banded preparations were analyzed.

Skin biopsies were taken from two subjects to compare cell proportion in the two tissues. The skin fibroblasts were processed for karyotyping at the second passage in both instances.

RESULTS

The results of analysis of chromosomal heteromorphisms are presented in table 1 and figures 1–4. Patient 1, a girl, had both maternal chromosomes 21 and a paternal no. 21 in her trisomic cell line, while her diploid cell line had only the maternally derived chromosomes 21 (fig. 1). Therefore, she apparently started as a trisomic zygote resulting from nondisjunction during the maternal first-

TABLE 1

SUMMARY OF DATA FROM FOUR MOSAIC DOWN SYNDROME PATIENTS

FAMILY NO.	AGE*	HETEROMORPHISMS OF CHROMOSOMES 21	INTERPRETATION	
			Trisomic† cell line	Disomic‡ cell line
1: Mother	30 yrs	*ab*	Mat I → Mat	
Father	36 yrs	*cd*		
Patient	2 yrs 9 mos	*abc/ab*		
2: Mother	26 yrs	*ab*	Pat I → Pat	
Father	27 yrs	*cd*		
Patient	4 yrs	*acd/cd*		
3: Mother	23 yrs	*ab*	Mat I → Mat	
Father	27 yrs	*bc*	or	
Patient	9 mos	*abc/ab*	Pat I → N	
4: Mother	28 yrs	*ab*	Pat II ⇄ N	
Father	31 yrs	*cd*		
Patient	5 days	*acc/ac*		

* Parental age at patient's birth. Patient's age at karyotyping.

† Mat I: Nondisjunction at maternal first meiosis. Pat I: Nondisjunction at paternal first meiosis. Pat II: Nondisjunction at paternal second meiosis.

‡ Mat: Maternal no. 21s transmitted. Pat: Paternal no. 21s transmitted. N: One chromosome 21 maternal and the other paternal in origin.

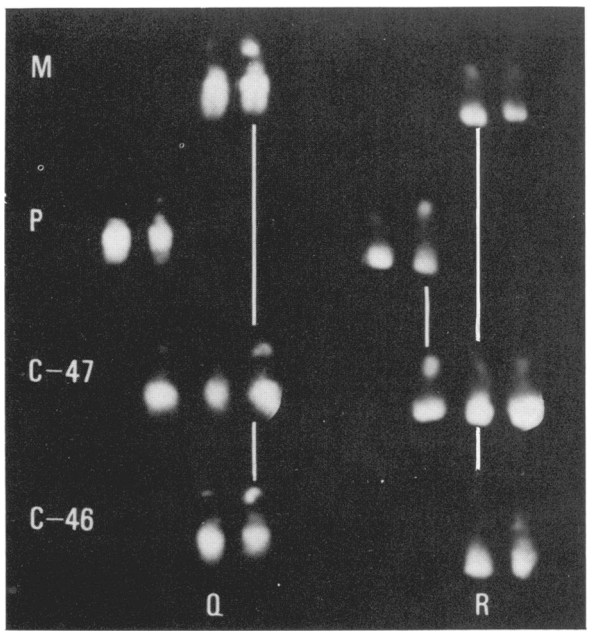

FIG. 1.—Transmission of marker chromosomes 21 from mother (*M*) and father (*P*) to the trisomic cell line (*C-47*) and to the diploid cell line (*C-46*) of the child with mosaic Down syndrome (patient 1). *Q*: Q-banded chromosomes 21; *R*: sequentially R-banded chromosomes 21 which are the same chromosomes as the Q-banded ones. *White lines* indicate the chromosome definitely inherited from one of the homologous members of a parent.

meiotic division, followed by an early-mitotic loss of the paternally derived chromosome 21. Patient 2, a boy, likewise started as a trisomic zygote originating from a paternal first-meiotic event, with a subsequent loss of the maternally inherited chromosome 21 (fig. 2). Patient 3, a boy, started as a trisomic zygote resulting from a first-meiotic event in either parent (fig. 3). Patient 4, a boy, could have originated from either a diploid zygote or a trisomic zygote resulting from a paternal second-meiotic error (fig. 4).

The heteromorphic patterns of chromosomes 3, 4, 13, 14, 15, and 22, as well as the sex-chromosome constitution, were identical between the diploid and trisomic cell lines in each of the four mosaic subjects studied, indicating that none of the mosaics was a diploid/trisomic chimera. There was no discrepancy between the chromosomal heteromorphic patterns of the mosaics and their fathers.

Repeat lymphocyte cultures from the four mosaic subjects did not show significant changes in the proportion of diploid and trisomic cell lines, with the exception of patient 4, whose share of diploid cell line increased from 24% at age 5 days to 49.2% at age 11 months (table 2).

Both peripheral blood lymphocytes and skin fibroblasts were analyzed in patients 1 and 3. In both, the proportion of trisomic cells was higher in skin fibroblasts than in peripheral blood lymphocytes: 81% vs. 16% in patient 1 and 100% vs. 6% in patient 2 (table 2).

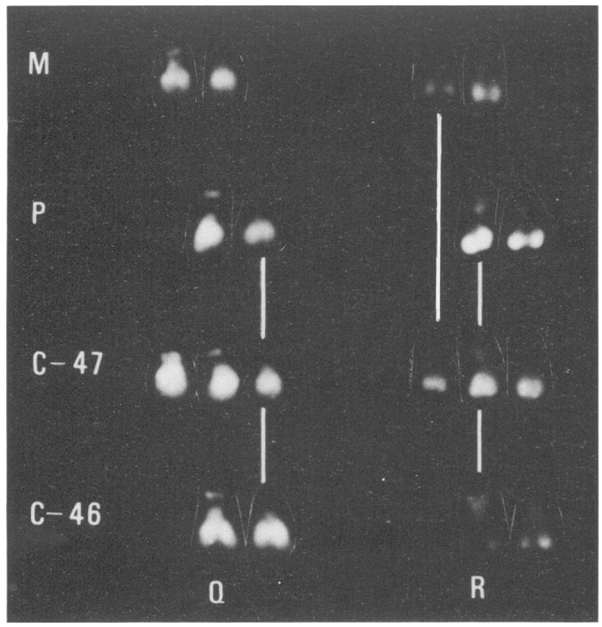

FIG. 2.—Transmission of marker chromosomes 21 in patient 2

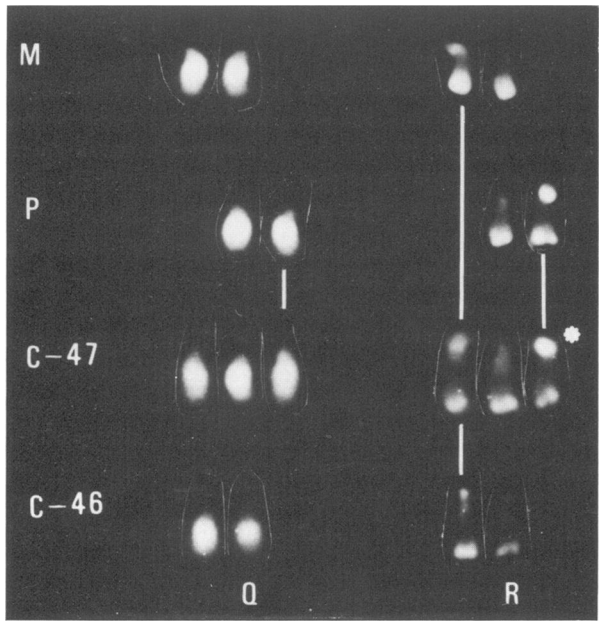

FIG. 3.—Transmission of marker chromosomes 21 in patient 3. *Asterisked chromosome in the trisomic cell line* was transmitted from father but this chromosome was not inherited to the diploid line.

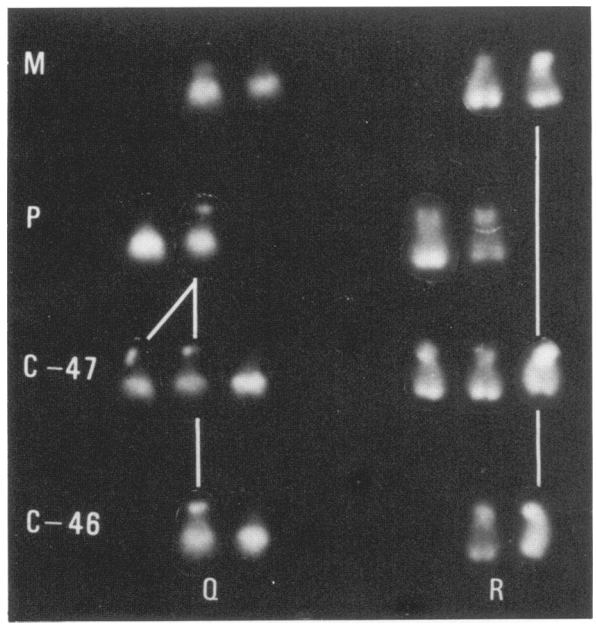

FIG. 4.—Marker chromosomes 21 in patient 4 and their parents

DISCUSSION

Of the four mosaic trisomy 21 patients studied, three apparently started as a trisomic zygote resulting from an error during meiosis, followed by the loss of a chromosome 21 during an early mitosis to result in a diploid/trisomic mosaic. In the remaining patient, it was not possible to determine whether the patient started as a trisomic or a disomic zygote. These results, although still preliminary, support the estimate by Richards [4], based on the maternal-age distribution in 125 mosaic mongols, that 80% of such mosaics arise from meiotic nondisjunction followed by a "normalizing" mitotic error.

Analysis of chromosomal heteromorphisms has only limited applicability to the problem since origin of a diploid/trisomic mosaic from a diploid zygote can be excluded but not proved. In terms of marker features, four types of trisomic/diploid mosaics are possible, namely, *aaa/aa*, *aab/aa*, *aab/ab*, and *abc/ab*. The first type is wholly uninformative. The second could have originated only from a trisomic zygote. The third, as in our patient 4, could have resulted from either a diploid or a trisomic zygote. The last type, as in our patients 1–3, again could have originated only from a trisomic zygote.

Our longitudinal studies on the proportion of diploid and trisomic lymphocyte cell lines over a period up to 15 months did not reveal a constant tendency. In patient 4 only, an increase of the diploid cell line was observed with passing time, possibly reflecting the fact that the patient was studied from the neonatal period. A more extensive longitudinal study by Taylor [8, 9], covering 18 patients with mosaic Down syndrome over periods up to 5 years, indicated that rapid cell

TABLE 2

DISTRIBUTION OF CHROMOSOME NOS. IN LYMPHOCYTE AND FIBROBLAST CULTURES FROM FOUR SUBJECTS WITH MOSAIC DOWN SYNDROME

			LYMPHOCYTES					SKIN FIBROBLASTS						
PATIENT NO.	ORIGIN	AGE	46*	46 (4G)	46* (5G)	47 (5G)	% normal cells†	Passage	Days in culture	46*	46 (4G)	46* (5G)	47 (5G)	% normal cells†
1	Mat I → Mat	15 mos	···	28	···	12	70							
		2 yrs 9 mos	2	84	···	16	84	2	60	1	18	2	79	19.6
2	Pat I → Pat	4 yrs	5	70	···	30	70							
		5 yrs	1	64	···	36	64							
3	Mat I → Mat	9 mos	···	63	1	3	95.5	2	23	···	···	···	31	0
	or	19 mos	3	97	···	3	97							
	Pat I → N													
4	Pat II ⇄ N	5 days	···	24	···	76	24							
		3 mos	1	28	···	72	28							
		11 mos	1	32	···	33	49.2‡							

* Random loss.
† Cells with random chromosome loss were excluded from calculation.
‡ Significant increase ($P < .005$).

selection occurs in young mosaic mongols. There was no general rule, however, and in some patients erratic fluctuations occurred.

A greater proportion of G trisomic cells in skin than in blood was observed in patients 1 and 3, as has often been reported in young mosaic mongols [10, 11]. Ford [11] suggested that the discrepancy results from a selective advantage of normal cells and is more apparent in tissues with a rapid turnover such as lymphocytes.

At least two, possibly three, of the four mosaic subjects studied had a diploid cell line that consisted of "uniparental" chromosomes 21, with both the homologs being inherited from a parent [12]. Yet, the uniparental disomic cell lines apparently did not suffer from selective disadvantage compared to the trisomic cell lines which had both maternally and paternally derived chromosomes 21.

As for mosaic trisomies of autosomes other than no. 21, we reported a 46,XX/47,XX, +22 abortus that apparently originated from a trisomic zygote, with the extra chromosome 22 coming from a maternal first-meiotic event [7]. A more recent abortion study included two normal/trisomy 16 mosaic abortuses apparently resulting from an error during the maternal first-meiotic division, and a normal/trisomy 4 mosaic abortus originating from a meiotic division in either parent [13]. There is obviously a need for further studies on the origin of mosaic autosomal trisomies, including mosaic trisomy 21.

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ADDENDUM

After submitting this paper for publication, we studied another newborn patient with the mosaicism. The proportion of trisomic cells was 13.3%. This mosaic originated from either a diploid zygote or a trisomic zygote resulting from a maternal second-meiotic error.

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